REMARKS

Claims 2-4, 16-18, 24, 25, 27, 30, 32 and 35-41 were pending in this application. Claims 27 and 41 are re-written in independent form. Accordingly, claims 2-4, 16-18, 24, 25, 27, 30, 32 and 35-41 are pending and presented for consideration.

Telephonic Interview

Applicant thanks Examiner DeBerry and Examiner Allen for the telephonic interview conducted on August 24, 2006, with Jeff Way, Brian Fairchild and Fangli Chen. During the interview, it was discussed whether there is a motivation to combine the teachings of cited references U.S. Patent No. 6,608,183 to Cox ("Cox") and U.S. Patent No. 5,888,772 to Okasinski *et al.* ("Okasinski") to carry out Applicant's invention. Examiner Allen acknowledged that, if the teachings of Cox focused on introducing "free" cysteines in erythropoietin, there could be no motivation to combine Cox and Okasinski. It was also discussed that the removal of the cysteine at position 33 promotes formation of the Cys_{29}-Cys_{88} disulfide bond. Applicant has incorporated the interview substance in this response.

Claim Rejections under 35 U.S.C. § 103 over Sytkowski in view of Cox and in further view of Okasinski

Claims 2-4, 16-18, 24, 25, 30, 32, 35 and 39 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Sytkowski *et al.* (WO 99/02709) in view of Cox and in further view of Okasinski. Specifically, the Office action alleges that it would be obvious for one of skill in the art to make the Fc-EPO fusion protein as suggested by Sytkowski and to modify the EPO portion with cysteine substitutions as suggested by Cox and Okasinski (*see, e.g.*, the Office action, page 4, the last paragraph). Applicant respectfully traverses the rejection for the reasons enumerated below.

35 U.S.C. §103 states that the subject matter, taken as a whole, must be considered when evaluating the patentability of an invention under 35 U.S.C. §103. The consistent criteria for the determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that the claimed subject matter should be carried out and would have a reasonable likelihood of success. Both the suggestion and the expectation of success must be found in the prior art, not in Applicant's disclosure. *In re Dow Chemical Company*, 837 F.2d 469,473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). One cannot use hindsight reconstruction to pick and

choose among isolated disclosures in the prior art to deprecate the claimed invention. *In re Fine*, 5 USPQ2d at 1600. Rather, there must be some teaching or suggestion supporting their use in the particular claimed combination. *See Smithkline Diagnostics, Inc. v. Helena Laboratories Corp.*, 859 F.2d 878, 887, 8 USPQ2d 1468, 1475 (Fed. Cir. 1988).

Applicant respectfully submits that the skilled artisan would not have been motivated to combine the teachings of the references, in particular, Cox and Okasinski, cited by the Office action to carry out Applicant's invention. Independent claim 30 is directed to an Fc-erythropoietin (Fc-EPO) fusion protein and requires that the erythropoietin (EPO) portion have a Cys at a position corresponding to Trp_{88} of human EPO and an amino acid other than Cys at a position corresponding to position 33 of human EPO such that the EPO portion contains a Cys_{29}-Cys_{88} disulfide bond. Cox teaches a method for adding or creating free cysteines onto growth hormones, including EPO, for site-specific conjugation with polyethylene glycol (PEG) or other such moieties (*see*, *e.g.*, column 3, lines 49-52). Although Cox teaches a cysteine substitution at position 88, Cox explicitly requires that the newly added cysteine must be free and accessible for PEGylation for his method to be successful (*see*, Cox, column 4, lines 27-31). For example, as set forth on column 4, lines 1-11, Cox states: "The preferred method for PEGylating proteins is to covalently attach PEG to cysteine residues using cysteine-reactive PEGs. . . . At neutral pH, these PEG reagents selectively attach to 'free' cysteine residues, i.e., cysteine residues not involved in disulfide bonds." [Emphasis added.] On column 4, lines 18-21, Cox states: "Cysteine residues in most proteins participate in disulfide bonds and are not available for PEGylation using cysteine-reactive PEGs." On column 4, lines 27-31, Cox further emphasizes: "The newly added 'free' cysteines can serve as sites for the specific attachment of a PEG molecule using cysteine-reactive PEGs. The added cysteine must be exposed on the protein's surface and accessible for PEGylation for this method to be successful." [Emphasis added.] Therefore, one of skill in the art upon reviewing Cox would not have been motivated to combine the teachings of Cox with that of Okasinski to construct a modified EPO in which the newly engineered cysteine forms a disulfide bond, as suggested by the Office action, because such a combination would defeat the intended purpose of the Cox invention. MPEP states: "If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." MPEP, § 2143.01 (V) citing *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

Accordingly, Applicant respectfully submits that the proposed combination of Cox and Okasinski represents a hindsight reconstruction of the invention rather than a proper rejection, based on the perspective of one skilled in the art, as required by § 103.

Applicant further submits, even if the disclosures of Sytkowski, Cox and Okasinski were combined, such a combination would not teach Applicant's invention as claimed in claim 30. As discussed above, claim 30 requires, *inter alia*, that the EPO portion of the Fc-EPO fusion protein contain a Cys at a position corresponding to Trp_{88} of human erythropoietin and an amino acid other than Cys at a position corresponding to position 33 of human erythropoietin such that the EPO portion comprises a Cys_{29}-Cys_{88} disulfide bond. Sytkowski teaches an Fc-EPO fusion protein. However, Sytkowski does not teach or suggest any cysteine substitutions in the EPO portion. Cox teaches a method for adding or creating free cysteines onto growth hormones, including EPO, for site-specific PEGylation (*see, e.g.*, column 3, lines 49-52). Specifically, in order to introduce free cysteines into EPO protein, Cox teaches adding free cysteines at certain amino acid positions including position 88 (*see, e.g.*, Cox, column 3, lines 13-27, and column 26, lines 45-51). Alternatively, as set forth on column 25, lines 59-64, Cox teaches: "A 'free' cysteine can be created by changing either cysteine-29 or cysteine-33 to another amino acid. . . . The remaining 'free' cysteine (cysteine-29 or cysteine-33) would be a preferred site for covalently modifying the protein with cysteine-reactive moieties." [Emphasis added.] Therefore, although Cox teaches cysteine substitution at position 88 or changing cysteine-33 to a non-cysteine amino acid as alternative embodiments to generate free cysteines, Cox does not teach or suggest a Cys at a position corresponding to Trp_{88} of human EPO and an amino acid other than Cys at a position corresponding to position 33 of human EPO such that the EPO portion comprises a Cys_{29}-Cys_{88} disulfide bond as required in claim 30. As discussed above, Cox also does not provide any motivation or incentive to one of skill in the art to combine a cysteine substitution at position 88 with a non-cysteine amino acid substitution at position 33 such that the cysteine at position 88 forms a disulfide bond with a cysteine at position 29 of human EPO.

Okasinski does not correct the deficiency of Cox. Okasinski relates to a double mutant of EPO protein in which a mutation at a first position, which causes a significant loss in activity, is compensated for by a mutation at a second position (*see, e.g.*, Okasinski, column 5, lines 1-10, and Example 10). Specifically, Okasinski teaches a (Cys^{139}, X^{39}) double mutant of EPO (X is a

non-cysteine amino acid) in which a substitution of cysteine for arginine at position 139, which causes a significant loss in activity, is compensated for by a second non-cysteine substitution at position 33. According to Okasinski, the (Cys^{139}, X^{39}) double mutant contains a Cys_{29}-Cys_{139} disulfide bond. Okasinski however does not teach or suggest the combination of a cysteine substitution at position 88 with a non-cysteine substitution at position 33 of human EPO as required in claim 30. Okasinski also does not provide any motivation or incentive to one of skill in the art that such a double mutant combination should be carried out and would have a reasonable likelihood of success.

Therefore, Applicant submits that the combination of Sytkowski, Cox and Okasinski, even if proper, does not teach or suggest an Fc-EPO fusion protein wherein the EPO portion contains a Cys at a position corresponding to Trp_{88} of human EPO and an amino acid other than Cys at a position corresponding to position 33 of human EPO such that the EPO portion comprises a Cys_{29}-Cys_{88} disulfide bond as required in claim 30.

Accordingly, Applicant submits claim 30 and any claims dependent therefrom are novel and unobvious over Sytkowski, Cox and Okasinski, either alone or in combination. Applicant therefore respectfully requests reconsideration and withdrawal of the rejection of claims 2-4, 16-18, 24, 25, 30, 32, 35 and 39.

Claim Rejections under 35 U.S.C. § 103 over Sytkowski in view of Cox and Okasinski and in further view of U.S. Patent No. 5,585,097 to Bolt et al. or U.S. Patent No. 5,935,824 to Sgarlato et al.

Claims 36-38 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Sytkowski in view of Cox and Okasinski and in further view of U.S. Patent No. 5,585,097 to Bolt *et al.* ("Bolt"). Claim 40 stands rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Sytkowski in view of Cox and Okasinski and in further view of U.S. Patent No. 5,935,824 to Sgarlato *et al.* ("Sgarlato"). Applicant traverses the rejections for the reasons enumerated below.

As discussed above, claim 30 and any claims dependent therefrom including claims 36-38 and 40 are novel and unobvious over Sytkowski, Cox and Okasinski, alone or in combination. Neither Bolt nor Sgarlato corrects the deficiency of Sytkowski, Cox or Okasinski discussed

above because the teachings of Bolt and Sgarlato are irrelevant to the cysteine variations in EPO protein.

Therefore, Applicant submits claim 30 and any claims dependent therefrom including claims 36-38 and 40 are novel and unobvious over Sytkowski, Cox, Okasinski, Bolt, and Sgarlato, either alone or in any combinations. Applicant therefore respectfully requests reconsideration and withdrawal of the rejections of claims 36-38 and 40.

Claim Objections

Claims 27 and 41 are objected to for depending from a rejected claim. Without acquiescing to the objection and solely to advance the prosecution, Applicant has re-written claims 27 and 41 in independent forms. Therefore, Applicant respectfully requests reconsideration and withdrawal of the objection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicant respectfully submits that pending claims 2-4, 16-18, 24, 25, 30, 32, 35 and 39 are in condition for allowance. The Examiner is invited to telephone the undersigned agent to discuss any remaining issues.

Respectfully submitted,

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